Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling.

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Public Summary:
The Hippo pathway is crucial in organ size control, and its dysregulation contributes to tumorigenesis. However, upstream signals that regulate the mammalian Hippo pathway have remained elusive. Here, we report that the Hippo pathway is regulated by G-protein-coupled receptor (GPCR) signaling. Serum-borne lysophosphatidic acid (LPA) and sphingosine 1-phospophate (S1P) act through G12/13-coupled receptors to inhibit the Hippo pathway kinases Lats1/2, thereby activating YAP and TAZ transcription coactivators, which are oncoproteins repressed by Lats1/2. YAp and TAZ are involved in LPA-induced gene expression, cell migration, and proliferation. In contrast, stimulation of Gs-couples receptors by glucagon or epinephrine activate Lats1/2 kinase activity, thereby inhibiting YAP function. Thus, GPCR signaling can either activate or inhibit the Hippo-YAP pathway depending on the coupled G protein. Our study identifies extracellular diffusible signals that modulate the Hippo pathway and also establishes the Hippo-YAP pathway as a critical signaling branch downstream of GPCR.

Scientific Abstract:
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